5/2

# ANALGESIC-ASSOCIATED KIDNEY DISEASE

National Institutes of Health
Consensus Development
Conference Statement
Volume 5 Number 2

NEWARK PUBLIC LIBRARY

MAY 13 1986

U. S. GOVT. PUBS.
DEPOSITORY 355

## Introduction and Conclusions

### *Introduction*

Ingestion of large amounts of some pain-relieving drugs over long periods of time has been shown to be associated with the development of one type of kidney disease that can lead to kidney failure. Since this problem was first reported in the 1950s, analgesic-associated kidney disease has become recognized as a significant, costly, and potentially preventable and treatable health problem. While research has shown an association of analgesic ingestion with kidney disease, there continues to be debate about the specific drugs that cause it, the mechanisms by which renal damage occurs, and the extent to which this illness may contribute to the overall burden of chronic renal disease in our society. The distributor and prevalence of analgesic-associated kidney disease appear to vary widely in different countries of the world and within the countries where it has been shown to occur.

In an effort to resolve some of the questions about this type of kidney disease, the National Institutes of Health convened a Consensus Development Conference on Analgesic-Associated Kidney Disease on February 27-29, 1984. After a day and a half of scientific presentations by experts of the available data about the problem, a Consensus Panel including representatives of the fields of nephrology, pathology, internal medicine, family medicine, pharmacology, biostatistics, and epidemiology, and of the general public considered the scientific evidence and agreed on answers to the following questions:

1. Can analgesics, alone or in combination, cause kidney disease and chronic kidney failure? What evidence supports these conclusions?
2. What are the scope and characteristics of the problem of kidney disease caused by excessive use of analgesics in the United States and in other countries?
3. What causes analgesic-associated kidney disease?
4. What factors increase the risk of occurrence of analgesic-associated kidney disease?
5. Can analgesic-associated kidney disease be prevented?
6. What treatment strategies are appropriate?
7. What are the directions for future research?

### *Panel's Conclusions*

Considerable evidence indicates that combinations of antipyretic analgesics, taken in large doses over a long period of time, cause a specific form of kidney disease and chronic renal failure. Persons so exposed may also be more susceptible to the subsequent development of uroepithelial tumors. In contrast, there is little evidence that preparations containing a single analgesic agent have been similarly abused and are similarly harmful.

The occurrence of analgesic-associated nephropathy shows striking geographical differences. Such differences may be related, at least in part, to regional variations in the habitual consumption of antipyretic-analgesic mixtures. The pathogenesis of the condition is uncertain but may involve a direct cytotoxic action of the analgesics on the renal papilla, perhaps enhanced by ischemia.

The sustained use of mixtures of antipyretic analgesics in large doses is not advisable. Serious consideration should be given to limiting over-the-counter products to those containing a single antipyretic-analgesic agent.

### 1.

### Can analgesics, alone or in combination, cause kidney disease and chronic renal failure? What evidence supports these conclusions?

The weight of evidence supports the view that combinations of antipyretic analgesics taken in large doses over long periods of time can cause kidney disease and chronic renal failure.

No evidence has been presented, however, to indicate that single antipyretic-analgesic drugs cause chronic renal disease when taken in the smaller doses usually prescribed by

***The National Institutes of Health urges that this summary statement be posted, duplicated, and distributed to interested staff.***

HE 20.3046:

physicians or taken for valid medical reasons in doses recommended by the manufacturer.

Three types of evidence support these conclusions.

1. *Clinical.* A characteristic clinical and pathological picture of a chronic tubulo-interstitial disease of the kidneys has emerged from many case reports. It is seen in patients who have consumed large quantities of antipyretic-analgesic mixtures, often in powder form. The disease is slowly progressive and commonly asymptomatic until severe renal failure occurs, although renal damage can be detected earlier by laboratory tests of the kidney's excretory or concentrating abilities. Papillary necrosis and interstitial scarring are characteristic; the disorder may be manifest clinically by urinary passage of necrotic tissue or by urography and signaled by sterile pyuria and low fixed urinary specific gravity.

The condition is seen mainly in women who take large doses of analgesic mixtures daily over long periods of time. Many of them may also exhibit gastrointestinal disorders, anemia, and emotional disturbances.

When persons with analgesic nephropathy stop ingesting analgesic mixtures, progression of the renal disease may be retarded or even reversed. In contrast, if they continue to consume the analgesics, the disease usually progresses.

2. *Epidemiological.* Although the epidemiological evidence is limited, certain studies, especially in areas of high consumption outside the United States, support an association between the heavy use of analgesic mixtures and chronic renal disease, particularly papillary necrosis. For example, in one geographic area, the relative risk for developing papillary necrosis was 17 times higher in heavy users than in nonusers. In another, prolonged use of phenacetin-containing analgesics by a group of working women studied over a 10-year period was associated with a significant increase in impaired renal function; an increased mortality from cardiovascular and renal disorders was also reported.

Analgesic nephropathy, including papillary necrosis, is most common in regions where the consumption and/or sale of analgesic mixtures is high. Furthermore, where the sale of such compounds has been effectively restricted, the prevalence of the disease appears to have diminished.

Certain evidence also suggests that very heavy and sustained use of some analgesic mixtures may predispose to cancer of the urinary tract, particularly transitional cell carcinoma of the renal pelvis.

3. *Experimental.* Large doses of analgesics, including aspirin, phenacetin, acetaminophen, and combinations of these, cause renal papillary necrosis in animals. The period of drug exposure in animal studies has been shorter than that in humans, while the dose necessary to produce injury has often been very high. For these and other reasons, the applicability of animal studies to human disease may be questioned; nevertheless, the demonstration in animals of a type of nephrotoxicity similar to that reported in humans lends weight to a causal association between analgesic abuse and kidney disease. The results of laboratory studies have suggested biochemical mechanisms by which phenacetin or its metabolites, as well as salicylates, may produce tissue damage in the kidney.

## 2.

## What are the scope and characteristics of the problem of kidney disease caused by excessive use of analgesics in the United States and in other countries?

Determining the magnitude and scope of the problem of analgesic-associated nephropathy is difficult. It is relatively easy to identify patients with analgesic nephropathy who have advanced or end-stage renal disease, but earlier or milder cases are difficult to identify. However, the latter must be taken into account to assess fully the potential public health problem.

The magnitude of the problem in its various degrees of severity can be viewed in at least three ways: the frequency of occurrence in the population at large, the frequency of occurrence in persons taking antipyretic analgesics, and the burden that treating the condition imposes on medical and financial resources.

*1. Frequency in the General Population.* In the United States, end-stage renal disease due to analgesic nephropathy is rare, occurring roughly on the order of one new case per million population per year. However, in some areas, such as parts of the Southeast, where the use of powders containing combinations of analgesics is more common, the incidence is higher, perhaps on the order of 10 per million per year. The incidence is also higher in areas of Belgium, Australia, and Scotland; in Switzerland, the crude incidence has been estimated to be as high as 15 per million per year.

Data on the incidence or prevalence of less severe analgesic nephropathy in the general population are limited, but its frequency is probably several times that of end-stage analgesic nephropathy.

*2. Frequency in Analgesic Users.* The proportion of analgesic users who develop analgesic nephropathy is not known. Evidence of at least moderately impaired kidney function was found to occur in a substantial proportion of a group of working women in Switzerland who took phenacetin-containing analgesics regularly.

There is no evidence that persons taking any antipyretic analgesics occasionally for headaches or other pains develop analgesic nephropathy. Similarly, advanced analgesic nephropathy is rare even among patients for whom regular or frequent use of analgesics is prescribed by physicians. The lack of data about the extent of use of these drugs in the

general population, particularly heavy use, makes it very difficult to correlate the occurrence of analgesic nephropathy with the amount of analgesics taken by individuals.

3. *Financial and Medical Care Burden.* In most of the United States, analgesic nephropathy accounts for about 2 percent of end-stage renal disease. In northwestern North Carolina, this figure may be as high as 10 percent. If we assume the 2-percent figure, the minimal cost of caring for such patients nationally would be at least $40 million per year, given an estimated annual cost for end-stage renal disease of $2 billion. Thus, even though severe renal failure due to analgesic nephropathy is infrequent in the United States, its financial impact on society is significant.

There are no data to indicate the undoubtedly substantial costs of care for less severe analgesic nephropathy.

## 3.

### What causes analgesic-associated kidney disease?

Four clinical and experimental features are relevant to the pathogenesis of analgesic nephropathy. (1) The disease is most commonly associated with the ingestion of analgesic mixtures in large doses over a prolonged time. (2) The initial lesion occurs in the papilla; changes in the cortex are secondary to papillary damage. (3) Papillary necrosis may be accentuated experimentally and in certain patients by dehydration and low urine volumes. (4) The major phenacetin metabolite, acetaminophen, as well as salicylates, is concentrated on the papilla, particularly during low urine output. These features suggest that the disease results from the effects of a toxic agent or agents in the renal papilla, but the precise pathogenetic mechanisms are still unclear.

Present evidence suggests that acetaminophen causes tissue injury as a result of its conversion to toxic metabolites. By lowering the concentration of glutathione, a substance that protects against such tissue injury, aspirin and other salicylates enhance toxicity. Salicylates and acetaminophen also inhibit prostaglandin synthesis and thus may, by reducing medullary blood flow, potentiate papillary damage. These data offer attractive though yet unproven explanations for the synergistic effects of phenacetin and aspirin in causing papillary necrosis. They also suggest avenues for research into interactions of other analgesic and anti-inflammatory drugs that may lead to renal disease.

## 4.

### What factors increase the risk of its occurrence?

Clinical studies suggest that the risk of developing analgesic nephropathy depends largely on the magnitude and duration of consumption of analgesic mixtures. This in turn is often influenced by cultural acceptance, promotion and availability of the drugs, occupational stress, and regional patterns of overuse of analgesics. Consumption of over-the-counter analgesic mixtures may be enhanced by the inclusion of stimulant drugs such as caffeine and the packaging of the compounds as powder. Additional risk factors, such as hot climate, laxative abuse, and genetic predisposition, have been suggested but not established.

## 5.

### Can it be prevented?

Current evidence suggests that the key to the prevention of analgesic nephropathy is to halt the inappropriate use of analgesics. It should therefore be possible to adopt measures to reduce its incidence substantially, as has already been undertaken in Canada.

Inasmuch as no therapeutic indication has been established for combining antipyretic-analgesic agents, serious consideration should now be given to the withdrawal of such mixed analgesic drugs from over-the-counter use in the United States. Such a measure appears to have reduced the occurrence of analgesic nephropathy in several countries. In Australia, however, when phenacetin in analgesic mixtures was replaced by either salicylamide or acetaminophen, the incidence of end-stage renal disease due to analgesic nephropathy did not fall.

Preparations containing single antipyretic analgesics such as aspirin or acetaminophen should remain available as over-the-counter medications, since there is no evidence that their occasional use is related to analgesic nephropathy. The risk from prolonged use of single-ingredient analgesics appears to be small. Patients who require prolonged high intake of analgesics, however, including nonsteroidal anti-inflammatory drugs, should be observed for the possible appearance of renal dysfunction at an early and potentially reversible stage. A high fluid intake, especially in warm climates, may be helpful in avoiding concentration of salicylates or acetaminophen in the renal papilla.

## 6.

### What treatment strategies are appropriate?

Patients with an established diagnosis of analgesic nephropathy should avoid taking antipyretic analgesics, especially of the mixed variety. If renal insufficiency is not advanced, renal function is likely to stabilize or even improve when analgesics are stopped. Even when renal insufficiency is well advanced, cessation of analgesic intake often slows the rate of loss of renal function.

The main strategies of management must include:

1. Avoidance of antipyretic-analgesic agents, as well as nonsteroidal anti-inflammatory drugs.
2. Prompt treatment of proven urinary tract infections.
3. Awareness that a necrotic papilla may slough and obstruct the

urinary tract, sometimes requiring prompt intervention to prevent further loss of renal function.

4. Careful supervision of hypertension.
5. Recognition that tumors of the urinary tract may occur more frequently in patients with analgesic nephropathy. Unexplained episodes of hematuria, including a marked increase in microscopic hematuria, should therefore be evaluated carefully.
6. Consideration of the non-renal manifestations of the analgesic abuse syndrome.

**7.**

## What are the directions for future research?

Epidemiological research is needed in several areas. More data are needed on the prevalence and extent of analgesic use, as well as the characteristics that predispose persons to heavy use and abuse, in each region of the United States. There is a need to evaluate the impact of measures designed to reduce analgesic abuse on the incidence of analgesic nephropathy. Moreover, it is important to establish the incidence of analgesic nephropathy in users of single-ingredient analgesics, as well as of nonsteroidal anti-inflammatory agents. Further basic epidemiological research is needed to elucidate the relationship between analgesic use and mild forms of the disease.

It seems possible that certain people are more susceptible than others to kidney injury from analgesics. Research is needed on the factors that may predispose patients to such injury. These include genetic constitution, variations in drug disposition, physiological factors such as hormonal status or state of hydration, sex, age, and environmental circumstances.

While some of the chemical reactions leading to the formation of cytotoxic metabolites have been characterized, further basic research is needed to study the nature of the toxic metabolites, the ultimate mechanisms of acute and chronic cell injury in various components of the papilla, the role of ischemic versus toxic factors, and the interactions among various drugs in causing papillary damage. More information is required on the relationship between analgesic nephropathy and uroepithelial cancer.

READEX FICHE

best copy available

**Members of the Consensus Development Panel were:**

Roscoe R. Robinson, M.D.
(Chairman)
Vice Chancellor for Medical Affairs
and Professor of Medicine
Vanderbilt University Medical Center
Nashville, Tennessee

Ramzi S. Cotran, M.D.
Mallory Professor of Pathology
Harvard Medical School
Pathologist-in-Chief
Brigham and Women's Hospital
Boston, Massachusetts

John S. Derryberry, M.D.
Past President
American Academy of Family
Physicians
Shelbyville, Tennessee

Jose A. Diaz-Buxo, M.D.
Medical Director
Metrolina Kidney Center
Charlotte, North Carolina

Michael Dunn, M.D.
Hanna Payne Professor of Medicine
Case Western Reserve University
School of Medicine
Director
Division of Nephrology
University Hospital
Cleveland, Ohio

Franklin H. Epstein, M.D.
Professor of Medicine
Harvard Medical School
Beth Israel Hospital
Boston, Massachusetts

Gary D. Friedman, M.D.
Assistant Director for Epidemiology
and Biostatistics
Department of Medical Methods
Research
Kaiser-Permanente Medical Care
Program
Oakland, California

James Grizzle, Ph.D.
Professor
Department of Biostatistics
University of North Carolina
School of Public Health
Chapel Hill, North Carolina

Robert G. Luke, M.D.
Director
Division of Nephrology and
Nephrology Research and Training
Center
University of Alabama
at Birmingham
Birmingham, Alabama

John M. Newmann, Ph.D.
President
National Association of Patients on
Hemodialysis and Transplantation
Health Management Consultant
Brookline, Massachusetts

James W. Russell, M.D.
Internist
Northeastern Vermont Regional
Hospital
St. Johnsbury, Vermont

Irwin M. Weiner, M.D.
Professor and Chairman
Department of Pharmacology
State University of New York
Upstate Medical Center
Syracuse, New York

**Members of the Planning Committee were:**

Nancy Boucot Cummings, M.D.
(Chairman)
Associate Director
Kidney, Urologic, and Hematologic
Diseases
National Institute of Arthritis,
Diabetes, and Digestive and
Kidney Diseases
National Institutes of Health
Bethesda, Maryland

James E. Balow, M.D.
Chief
Clinical Nephrology Service
Senior Investigator
National Institute of Arthritis,
Diabetes, and Digestive and
Kidney Diseases
National Institutes of Health
Bethesda, Maryland

William M. Bennett, M.D.
Professor of Medicine and
Pharmacology
Division of Nephrology
Oregon Health Sciences University
Portland, Oregon

James Bilstad, M.D.
Deputy Director (Medical Affairs)
Office of Biologics, Research and
Review
Food and Drug Administration
Rockville, Maryland

Vardaman M. Buckalew, Jr., M.D.
Professor of Medicine and Physiology
Bowman Gray School of Medicine
Winston-Salem, North Carolina

Martin Goldberg, M.D.
Taylor Professor of Medicine
Director
Department of Internal Medicine
University of Cincinnati
Medical Center
Cincinnati, Ohio

Robert H. Heptinstall, M.D.
Baxley Professor of Pathology
Johns Hopkins University
School of Medicine
Johns Hopkins Hospital
Baltimore, Maryland

Judith K. Jones, M.D., Ph.D.
Special Assistant to the Director
Office of Epidemiology and
Biostatistics
National Center for Drugs and
Biologics
Food and Drug Administration
Rockville, Maryland

Fitzhugh Mullan, M.D.
Chief Medical Officer
Office of Medical Applications
of Research
Office of the Director
National Institutes of Health
Bethesda, Maryland

Roscoe R. Robinson, M.D.
Vice Chancellor for Medical Affairs
and Professor of Medicine
Vanderbilt University Medical Center
Nashville, Tennessee

---

M. J. Scherbenske, Ph.D.
Program Director
Renal Physiology/Pathophysiology
National Institute of Arthritis,
Diabetes, and Digestive and
Kidney Diseases
National Institutes of Health
Bethesda, Maryland

James N. Fordham
Writer/Editor
Office of Health Research Reports
National Institute of Arthritis,
Diabetes, and Digestive and
Kidney Diseases
National Institutes of Health
Bethesda, Maryland

Michael J. Bernstein
Director of Communications
Office of Medical Applications
of Research
National Institutes of Health
Bethesda, Maryland

**The conference was sponsored by:**

National Institute of Arthritis,
Diabetes, and Digestive and
Kidney Diseases
Diseases
Lester B. Salans, M.D.
Director

Office of Medical Applications
of Research
J. Richard Crout, M.D.
Director

☆ U.S. GOVERNMENT PRINTING OFFICE : 1986 O - 152-846

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
National Institutes of Health
Office of Medical Applications of Research
Building 1, Room 216
Bethesda, MD 20205

Third Class Bulk Rate
Postage and Fees Paid
National Institutes of Health
Permit No. G29

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service National Institutes of Health